

Best practice in the management of benign prostatic hyperplasia in the patients requiring anticoagulation

Joshua Heiman, Tim Large and Amy Krambeck

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Abstract: In today's aging population, urologists are often treating older patients with multiple comorbidities. Lower urinary tract symptoms from benign prostate hyperplasia (LUTS/BPH) is a common condition that affects men, with increasing prevalence as men age. In a subset of patients, the symptoms are too severe or refractory to medical therapy and, therefore, surgical therapy is required to improve their LUTS. The use of medical therapy often delays the need to intervene surgically in men with LUTS/BPH and with advances in the management of cardiovascular disease, urologists are increasingly encountering more men requiring BPH surgery on chronic anticoagulation therapy. The decision of when to offer surgical intervention and how to manage anticoagulation medication in the perioperative setting is a dilemma with which surgeons are dealing with increasing frequency. The purpose of this review is to clarify the optimal approach to the surgical patient with LUTS/ BPH requiring anticoagulation therapy.

Keywords: lower urinary tract symptoms (LUTS), benign prostate hyperplasia (BPH), anticoagulation therapy, antiplatelet therapy, surgical interventions

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Introduction

In populations where life expectancy is increasing, the prevalence of lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH) is on the rise.¹ Additionally, although medical therapy is effective at mitigating immediate LUTS, it often does not cure the underlying condition and delays intervention.¹ As a result, urologists are faced with treating older patients with multiple comorbidities refractory or intolerant of BPH medications in need of surgical intervention for LUTS/BPH. This aging population of men suffering from LUTS/BPH often has concurrent cardiovascular diseases requiring anticoagulation (AC) or antiplatelet (AP) therapy.² The challenge of when to offer surgical intervention, which BPH surgery to perform, and how to manage blood thinners in the perioperative period is common among practicing urologists. In fact, in 2017, a survey completed by members of the Endourological Society found that the majority of BPH surgeons prefer to continue some form of anticoagulant therapy, in most cases, low-dose

aspirin, during BPH procedures.³ In this review, we aim to clarify the approach to surgical management of BPH in the anticoagulated patient.

Current anticoagulants/antiplatelets

Prior to the advent of direct oral anticoagulants (DOACs) in 2010, there were limited therapeutic options for patients requiring AC therapy. Vitamin K antagonists such as warfarin were the mainstay of therapy in secondary stroke prevention for atrial fibrillation and venous thrombosis prevention. The use of warfarin posed a challenge for clinicians due to its multiple interactions with food and medications. DOACs, also referred to as novel anticoagulants, reduced the involvement of clinicians and patients in the treatment and monitoring of AC therapy by decreasing the need for routine lab monitoring and reducing the number of drug–drug and diet interactions with therapy. Additional benefits of DOACs included shorter therapeutic half-life, and fewer major bleeding complications compared with warfarin.⁴

Correspondence to:
Amy Krambeck
Indiana University School
of Medicine, IU Health
Physicians Urology,
1801 N. Senate Blvd.,
Indianapolis, IN 46202-
5114, USA
akrambeck@iuhealth.org

Joshua Heiman
Tim Large
Indiana University,
Indianapolis, USA

Examples of DOACs include direct factor Xa inhibitors such as: rivaroxaban (Xeralto®, Janssen Ortho LLC Gurabo, Puerto Rico or Bayer AG Leverkusen, Germany), apixaban (Eliquis®, Bristol-Myers Squibb Company, Princeton, NJ), Enoxaparin (Lovenox®): sanofi-aventis U.S. LLC, Bridgewater, NJ, Enoxaparin (Lovenox, sanofi-aventis U.S. LLC Bridgewater, NJ) and direct thrombin inhibitors like dabigatran (Pradaxa®, Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT) (Table 1). Though DOACs provide much benefit, they do have disadvantages, such as a lack of reversal agents for factor Xa inhibitors, and only recently was idarucizumab approved by the US Food and Drug Administration for reversal of dabigatran.⁵ Like warfarin, the current indications for DOAC treatment are venous thromboembolism (VTE) prevention, embolic stroke prevention in nonvalvular atrial fibrillation, and prevention of VTE after orthopedic surgery.⁶

As opposed to anticoagulants, AP therapy continues to be the principal treatment to reduce risk of thrombosis of coronary stents or coronary artery bypass grafts (CABGs). Primary and secondary prevention treatment of ischemic heart disease postcoronary stenting or CABG includes dual AP therapy of aspirin with a P2Y₁₂ inhibitor, most commonly, clopidogrel. According to the updated 2016 American College of Cardiology guidelines, dual AP therapy should be given for at least 12 months in patients with recent acute coronary syndrome treated with either CABG or percutaneous coronary stenting.⁷

Current guidelines/recommendations

In 2014, the American Urological Association (AUA) published a review paper on AC and AP therapy in urological practice. The review suggests that a multidisciplinary approach to the management of antithrombotic medications in patients with recent thromboembolic events, mechanical valves, atrial fibrillation and cardiac stents reduces high morbidity and mortality when managing medications.⁸ According to the review paper, no elective procedure should be performed in patients within 1 year after placement of bare metal or drug-eluting stent. In the setting of BPH surgery, low-dose aspirin should be continued perioperatively in patients with cardiac risk factors because the data suggest no increased risk of major bleeding. Most relevant, the bleeding risk for patients who require continuation of aspirin for laser

prostate outlet procedures is significantly low.⁸ The AUA best practice review states that there is not enough evidence to determine the best time to resume anticoagulant therapy postoperatively except that therapy be resumed once the bleeding risk has decreased.⁸ The 2018 AUA surgical management of LUTS attributed to BPH guidelines recommend that holmium or thulium laser enucleation (HoLEP/ThuLEP) or GreenLight photovaporization (PVP) be considered in patients who are at higher risk of bleeding, specifically those on AC drugs.⁹

According to the 2018 European Association of Urology (EAU) guidelines for treatment of non-neurogenic male LUTS, all types of laser prostatectomy seem to be safe in chronically anticoagulated patients. The guidelines concluded that PVP (532 laser) is safe and effective, HoLEP has been performed safely, diode laser is an alternative and thulium laser is safe as well.¹⁰

Procedures

Transurethral resection of the prostate

Transurethral resection of the prostate (TURP) is still the most common surgical intervention offered for LUTS/BPH.³ The most common practice, before TURP, is to discontinue all oral AC or AP therapy for a few days prior to surgery and to preoperatively bridge with heparin or low-molecular-weight heparin (LMWH) therapy.¹¹ Descaseaud and colleagues studied the impact of oral AC on the morbidity of patients undergoing TURP and found that chronic oral AC has a significant impact on bleeding complications, duration of hospitalization and thromboembolic events. Duration of hospitalization was 6.4 days in the anticoagulated group *versus* 4.7 days in the control group, while bladder clots occurred in 13% of anticoagulated groups *versus* 4.7% in nonanticoagulated group.² Ong and colleagues reported that chronic anticoagulated patients who underwent enoxaparin bridging had higher risk of bleeding complications (44%) when compared with no oral AC (8%). Additionally, patients continuing perioperative AP therapy had a higher complication rate (17%) *versus* patients who stopped (4%) therapy. These complications included requiring continuous bladder irrigation (CBI) greater than 2 days and clot retention necessitating catheter reinsertion. Patients on oral AC also had significantly higher thromboembolic

complications and prolonged hospital stay when compared to non-anticoagulated patients.¹² A retrospective study by Taylor and colleagues found higher bleeding complication rates in patients continuing AP therapy or in chronically anticoagulated patients undergoing TURP (26.3% *versus* 9.8%). Most importantly, the study found that patients who withheld their oral AC preoperatively had significantly higher rates of cardio and cerebrovascular complications.¹³ The AUA best practice review paper suggests that due to the high rate of bleeding complications in oral AC patients undergoing TURP that that alternative bladder outlet procedures, such as laser therapy, be offered.⁸

Laser ablation

Overall, laser ablative procedures of the prostate have been found to be safe and effective in the anticoagulated patient.¹⁴ Chung *et al.* analyzed 162 men undergoing 532 nm PVP while on chronic AC. Of the patients 19% were on warfarin, 62% on asa, 12% were on clopidogrel and 7% were on 2 or more anticoagulants. All anticoagulants were continued at time of surgery except warfarin which was stopped 1–3 days preoperatively. Average age was 72 years with a mean transrectal ultrasound volume measurement of 91 g. There were no significant differences in length of stay between the control and anticoagulated groups (1.1 days *versus* 1.2 days). Delayed bleeding requiring CBI occurred in six (3.7%) patients and three of these required a blood transfusion. Reoperation for clot evacuation and fulguration of bleeding was required in one (0.6%) patient. The study concluded that PVP in patients with systemic AC is safe and effective.¹⁵ Another study by Woo and colleagues assessed patients undergoing PVP while continuing therapeutic levels of warfarin. There were no reported secondary surgeries or blood transfusions, although two (4.7%) patients required prolonged catheterization for bleeding. One (2.3%) patient was readmitted for a secondary bleed that was managed with bladder irrigation alone. The study concluded that PVP is safe, with good early outcomes in patients on therapeutic levels of warfarin.¹⁶ Ruszat and colleagues evaluated the outcomes of 500 GreenLight PVP procedures at a single center, of which, 225 patients underwent PVP while continuing AC therapy. Forty-three patients required postoperative CBI for hematuria, but, no blood transfusions were needed. The authors concluded that PVP is

safe and effective in high-risk patients, especially those actively on AC.¹⁷

Knapp and colleagues compared adverse events in men undergoing PVP with or without continued AC. PVP was performed in 59 patients with continued antithrombotic therapy (7% heparin, 44% warfarin, 34% clopidogrel, 1.5% dipyridamole-aspirin, 15% novel oral anticoagulant (NOAC), 3% clopidogrel and warfarin) and 272 patients who were not on antithrombotic therapy. There was no difference in total operation or laser time between the two groups, but the antithrombotic group was found to have significantly longer length catheter-dwelling times (32.4 h *versus* 15.6 h) and hospital length-of-stay days compared with the control group (46.6 *versus* 23.1). No patient required a blood transfusion. There was no significant difference between groups when comparing overall adverse events, but there was a higher rate of high-grade adverse events in the antithrombotic group (grade IIIa sepsis 5% *versus* 0.7%, bladder neck contracture 3.4% *versus* 0.4%, and grade IVb sepsis 1.7% *versus* 0%). The study concluded that continuing AC at time of PVP is not associated with an overall increased risk of adverse events; however, it is associated with higher-grade risks.¹⁸ Thus, PVP is safe to perform in the actively anticoagulated patient but should be carried out with caution.

Laser enucleation

HoLEP has been proven safe and effective in anticoagulated patients.¹⁹ In 2006, Elzayat and colleagues published one of the first studies assessing the safety of HoLEP in patients on antithrombotic therapy. A total of 81 patients were on AC; 14 underwent HoLEP without withdrawal of oral anticoagulants, 34 were with LMWH bridging, and 33 stopped 5 days prior surgery without bridging. Mucosal bladder injury and capsular perforation occurred in two and one patients, respectively. One patient who did not stop clopidogrel required intraoperative platelet transfusion due to bleeding, and morcellation was postponed because of decreased vision. Blood transfusion was required postoperatively in seven patients (8.4%). Three patients (3.6%) had clot retention and required rehospitalization for CBI within 2 weeks of surgery. The study compared these complication rates with TURP and determined that complication rates with HoLEP in the anticoagulated patient were considerably lower. The authors concluded that the hemostatic

Table 1. Common anticoagulant/antiplatelet medications encountered by urologists.²⁴

	Warfarin	Dabigatran (Pradaxa®)	Rivaroxaban (Xarelto®)	Apixaban (Eliquis®)	Enoxaparin (Lovenox®)	Clopidogrel (Plavix®)
Target	Vitamin K epoxide reductase	Thrombin	Factor Xa	Factor Xa	Antithrombin III	ADP (P2Y12)
Half-life (h)	20–60	12–17	5–9	9–14	4.5	N/A
Onset of peak effect (h)	72–96	2	2–3	3	3–5	2–8
Duration of action	2–5 days	24–36 h	24 h	24 h	24 h	7–10 days
Metabolism	Via cytochrome P450	Via P-glucoprotein transporter	Via cytochrome P450 (30%) and via P-glucoprotein transporter	Via cytochrome P450 (15%) and via P-glucoprotein transporter	metabolized in the liver by desulfation and depolymerization	Via cytochrome P450 (15%) 85% inactive
ADP, adenosine diphosphate.						

Table 2. Bleeding complication and transfusion rates in comparative studies on patients requiring anticoagulation.

Study	Year	Procedure	n	Bleeding complication rate (%)	Transfusion rate (%)	Level of evidence
Descazeaud <i>et al.</i> ²	2011	TURP	206	15	1.9	II
Ong <i>et al.</i> ¹²	2015	TURP	126	12.6	2.4	II
Taylor <i>et al.</i> ¹³	2011	TURP	72	2.6	5.5	II
Ruszat <i>et al.</i> ¹⁷	2008	PVP	222	9.8	0	II
Chung <i>et al.</i> ¹⁵	2011	PVP	162	4	2	II
Woo <i>et al.</i> ¹⁶	2011	PVP	43	4.7	0	II
Knapp <i>et al.</i> ¹⁸	2017	PVP	59	1.7	0	II
El Tayeb <i>et al.</i> ²¹	2016	HoLEP	116	0	3.5	II
Bishop <i>et al.</i> ²²	2013	HoLEP	52	0	7.7	II
Elzayat <i>et al.</i> ²⁰	2006	HoLEP	83	3.6	8.4	II
HoLEP, holmium laser enucleation; PVP, GreenLight photovaporization; TURP, transurethral resection of the prostate.						

properties of the holmium laser allow HoLEP to be safer and effective when compared with other BPH treatment options on anticoagulated patients. Specifically, the low depth of penetration of the holmium laser limits eschar formation which can contribute to delayed bleeding seen with other BPH procedures.²⁰

El Tayeb and colleagues compared 116 patients taking AC therapy with 1558 nonanticoagulated patients who underwent HoLEP at their institution. There was no difference in specimen weight between groups (69.8 g in the AC group *versus* 68 g in the control). There was no significant difference in both enucleation (51 min *versus*

65 min, AC *versus* control, respectively) and morcellation (5 g/min *versus* 4.5 g/min AC *versus* control, respectively) times between cohorts. There was no difference in postoperative outcomes except for longer length of stay (27.8 h *versus* 24 h) and duration of CBI (15 h *versus* 13.5 h) in the anticoagulated group, which was of low clinical significance. The transfusion rate was not significantly different (3.5% anticoagulated *versus* 1.6% control) and only two patients (1.9%) in the anticoagulated HoLEP group required clot evacuation *versus* 10 (0.7%) in the control group.²¹

Bishop and colleagues compared the immediate postoperative outcomes in patients with and without AC therapy undergoing HoLEP.²² The authors compared 52 patients on antithrombotic therapy at the time of HoLEP with 73 patients not on anticoagulant therapy at time of HoLEP. The median length of hospital stay was longer in the antithrombotic group (2 days *versus* 1 day). Blood transfusion was required in four (7.7%) patients *versus* none in the nonanticoagulated group.²² Studies such as the ones highlighted from Bishop and colleagues²² and El Tayeb and colleagues²¹ confirm that HoLEP is a safe and feasible treatment option for patients with large-gland BPH on anticoagulant or AP therapy requiring surgical intervention.

Thulium laser vapoenucleation (ThuVEP) and thulium laser enucleation (ThuLEP) utilize a similar technique as HoLEP, and the AUA guidelines recommend them as alternative to HoLEP in medically complex patients, specifically those requiring AC.⁹

Open simple prostatectomy and robotic simple prostatectomy

There are no studies or case reports within the literature evaluating the safety of open prostatectomy or robotic simple prostatectomy (RASP) in patients on AP/AC. In 2008, Krane and colleagues compared outcomes of patients undergoing robotic radical prostatectomy (RALP) who required AC therapy *versus* standard nonanticoagulated patients. Though the surgical technique of RALP compared to RASP is significantly different, the risk of bleeding and bleeding sequelae can be considered equivalent and thus RALP in patients on AC can be considered a surrogate for potential outcomes of RASP on AC. Patients on AC in this study either discontinued AC 7 days prior or were bridged with LMWH for 3 days before surgery. The authors found 6.7% transfusion rate

compared with 1.7% in standard patients. Readmission rates (5% *versus* 0.6%) were higher after RALP in the anticoagulated population compared with standard patients.²³ More data are needed prior to advocating AC bridging and RASP for men with LUTS due to large-gland BPH.

Novel/emerging therapies

New minimally invasive novel therapies for BPH lack evidence for specific recommendation on the management of antithrombotic therapy. To our knowledge, there are no published studies or data specifically focusing on the safety of UroliftTM, RezumTM, AquablationTM and prostate artery embolization in patients requiring AC. The use of these modalities to surgically treat LUTS/BPH in anticoagulated patients was not commented on in the 2018 AUA guidelines on BPH.

Conclusion

As longevity improves and prevalence of cardiovascular disease increases, urologists should anticipate a rise in surgical consultations for LUTS/BPH in patients on antithrombotic therapy. According to the AUA best practice statement and published data, laser enucleation and ablation procedures such as HoLEP and PVP provide clinicians with the safest surgical management options for BPH in patients requiring chronic antithrombotic medication (Table 2). The decision on how to manage these patients should utilize a multidisciplinary approach involving the urologist, cardiologist, primary care and anesthesiologist to develop a patient-specific management plan.

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Conflict of interest statement

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